Dose-Response Relationships for Radiation-Induced Hyperparathyroidism*

ARTHUR B. SCHNEIDER, THERESA C. GIERLOWSKI, EILEEN SHORE-FREEDMAN, MARILYN STOVALL, ELAINE RON, AND JAY LUBIN

Division of Endocrinology and Metabolism, Michael Reese Hospital, University of Illinois (A. B.S., T.C. G, E. S.-F.), Chicago, Illinois 60616; the Department of Radiation Physics, University of Texas, M. D. Anderson Cancer Center (M.S.), Houston, Texas 77030; and the Radiation Epidemiology Branch (E. R.) and Biostatistics Branch (J.L.), National Cancer Institute, Bethesda, Maryland 20892

ABSTRACT

It has been hard to establish with certainty that radiation exposure is a risk factor for developing hyperparathyroidism. In part this is because many cases of hyperparathyroidism remain asymptomatic and escape clinical detection. We present results from a study of 2555 subjects who received external beam radiotherapy to the head and neck area for benign conditions before their 16th birthday between 1939 and 1962. The average length of follow-up was 36.6 yr. There were 36 confirmed cases of hyperparathyroidism. Based on a relative

risk model, the excess relative risk increased significantly by 0.11/ centigray; however, the confidence interval was wide (95% confidence interval, 0.0–17.2). The hyperparathyroidism rates and dose-response relationships were not affected by gender or age at first radiation treatment. The demonstration of a dose-response relationship within an irradiated cohort supports an association between radiation exposure and hyperparathyroidism and suggests that the calcium levels of individuals irradiated to the head and neck area should be monitored. (*J Clin Endocrinol Metab* **80**: 254–257, 1995)

HYPERPARATHYROIDISM is generally considered one of the conditions arising in radiation-exposed individuals, but the evidence supporting this conclusion is limited. In part this is because hyperparathyroidism may be clinically undetected for a long period of time. Fujiwara *et al.* (1) studied 3948 atomic bomb survivors and found that hyperparathyroidism developed in 3 of 1583 nonexposed and 16 (compared to 4.8 expected) of 2365 exposed individuals. Tisell *et al.* (2) reported 63 cases of hyperparathyroidism in 444 people treated with x-rays for tuberculous cervical adenitis. In both studies a significant dose-response was noted. The relationship between radiation and hyperparathyroidism is supported by a number of case-control studies (3-6). However, these studies do not allow risk estimates to be calculated, and they are limited by the well known problem of obtaining an accurate history of childhood radiation exposure, especially among the controls.

We are studying a cohort of patients who were irradiated for benign head and neck conditions before their 16th birthday at Michael Reese Hospital in Chicago (7). Our previous observations of hyperparathyroidism in this cohort were based on comparisons with general population rates (8). As we recently estimated thyroid gland doses for individual study subjects (7), we now can examine the dose-response relationship for hyperparathyroidism. The findings confirm the association between radiation and hyperparathyroidism,

provide an estimate of the excess relative risk, and permit an analysis of other risk factors.

Subjects and Methods

Population at risk

The population at risk consists of 4296 patients who received external beam radiation therapy at our institution between 1939 and 1962 for benign conditions in the head and neck area before their 16th birthday. Criteria for including subjects in the cohort, screening efforts, and thyroid dosimetry were described recently (7). The dose estimates established for the thyroid are used here as estimates of the average dose to the parathyroids.

Follow-up

Of the 3843 subjects for whom dosimetry was completed, 2555 have been located and have provided information concerning nonthyroid tumors and their general health. All reports of parathyroid tumors and hyperparathyroidism were confirmed by reviewing records of any calcium and PTH measurements as well as any surgical and pathology records. Hyperparathyroidism was defined as elevated calcium with an elevated PTH level (above the upper limit of normal established by the individual laboratory) or surgical correction of hypercalcemia by the removal of one or more parathyroid glands. Cases in which parathyroid enlargement was encountered during the course of thyroid surgery and the preoperative calcium level was normal or unknown were excluded from the current analysis. For patients with hyperparathyroidism, person years at risk (P-yr) were calculated from the time of initial radiation exposure until surgery or, for those without surgery, until the date of diagnosis. For subjects without hyperparathyroidism, P-yr were accrued until the end of follow-up or August 1, 1993, whichever came first.

Statistical methods

Poisson regression methods were used to fit a relative risk model. Maximum likelihood parameter estimates, score tests for nested models, and likelihood-based confidence intervals were obtained using the Amfit regression program (9). Details of the models were previously de-

scribed (7). The data were cross-classified by sex, age at radiation treatment (<1, 1-4, 5-9, 10-14, and >=15 yr), radiation dose to the parathyroids in centigrams (<5, 5-9, 10–14,15-19, 20–29,30-39, ... , 90-99, 100-199, and >=200 cGy), time since treatment (0–4, 5-9, ... and >=45 yr), and calendar year intervals for date of last follow-up (1935-39, ... , 1965-69, 1970-73, 1974–79, 1980-1984, and >=1985), For each cross-classification cell, the number of observed cases of hyperparathyroidism and P-yr and P-yr-weighted means for several variables were computed (9).

Results

Of the 2555 subjects with completed dosimetty and follow-up, 36 (1.41%) developed clinically confirmed hyperparathyroidism. Twenty-six patients had surgically confirmed adenomas, including 1 with adenomas in more than 1 gland surrounded by normal parathyroid tissue. Another 5 had parathyroid hyperplasia, and 2 had surgery with pathological findings that did not allow classification as adenoma or hyperplasia. Three patients had hyperparathyroidism, but did not undergo surgery. All but 1 of the cases received radiation treatment to the tonsils and nasopharynx, the most common site of treatment in this cohort, and 4 received 2 courses of treatment. Seven of the cases had a history of kidney stones, 1 had a history of peptic ulcer disease, and 2 had a less well defined history of gastrointestinal problems. There were 4 parathyroid adenomas not included in the analysis; 3 were associated with normal calcium levels, and 1 was of unknown function.

The mean ages at occurrence were 41.7 yr for men and 39.8 yr for women. As shown in the cumulative probability plot for hyperparathyroidism (Fig. 1), the first case was diagnosed and operated upon 20 yr after the initial radiation exposure. Hyperparathyroidism continues to occur and by the end of follow-up, the fraction of patients with hyperparathyroidism approaches 5%.

The overall crude rate of hyperparathyroidism was 3.9 cases/10^4P-yr (Table 1). After adjusting to reflect persons with attained age of 35-45 yr, the rate of hyperparathyroidism was 9.4 cases/10^4P-yr. The adjusted rates did not vary significantly by gender or age at first radiation treatment, but the rates did increase with increasing time (calculated as attained age, years since treatment, or calendar year).

The mean parathyroid dose for the 36 cases was 77.1 cGy, compared to 58.3 cGy for the entire study cohort. For the 26

Table 1. Numbers of hyperparathyroidism cases, adjusted rates, and tests of significance for main effects

	No. of cases	Adjusted rate X 10^{4a}	P value
Overall	36	9.4	
Sex			
Males	19	8.6	0.59
Females	17	10.3	
Age at Rx (yr)			
<5	25	11.4	0.27
>=5	11	6.4	
Attained age (yr)			
<35	11	1.4	<.001
35–44	13	9.4	
>=45	12	33.8	
Yr since Rx			
<30	9	1.4	0.02
30-39	14	9.2	
>=40	13	25.4	
Calendar year			
<1974	2	0.3	<.001
1974–1979	13	10.0	
>= 1980	21	16.7	

^{a} Adjusted to reflect persons with attained ages 35–44 yr. The crude overall rate is 3.9/10^4P-yr.

patients with parathyroid adenomas, the mean dose was 83.6 cGy. Although we used a single dose for the parathyroid glands, the superior glands received a larger dose than the inferior glands because the radiation was directed to the posterior pharynx. The distribution of the 27 parathyroid adenomas (in 26 patients) was 16 in the superior location (10 left and 6 right) and 11 in the inferior location (5 left, 5 right, and 1 mediastinum). The most consistently reported characteristic of the adenomas was their largest dimension (available for 13 superior and 8 inferior adenomas). By this measure, the superior adenomas tended to be larger (21 mm compared to 18 mm). Neither this difference nor the difference between the observed locations of the adenomas and random locations was statistically significant.

The distribution of cases, disease rates, and relative risks by radiation dose is given in Table 2. As there was no group of nonirradiated subjects undergoing comparable follow-up, the group that received parathyroid doses of less than 50 cGy was used for comparison. The dose-response relationship is shown in Fig. 2. Although the point estimate of the dose response [excess relative risk (ERR)/cGy] is large, the lower confidence limit is zero. The risk pattern does not appears to
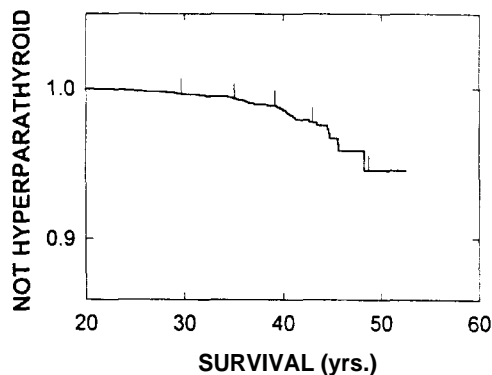

FIG. 1, Kaplan-Meier cumulative probability plot for hyperparathy-roidism (10). The *intersecting vertical lines* indicate decrements of 500 subjects from the 2555 initially at risk.

Table 2. Cases of hyperparathyroidism, P-yr risk, rates, and relative risks (RR) by dose categories

	Dose (cGy)				
	<50	50–59	60–69	≥70	Total
Cases	8	15	5	8	36
P-yr	28,153	29,744	14,639	21,037	93,573
Mean dose (cGy)	34.9	52.4	64.3	100.4	58.3
Rate × 10^4	2.8	5.0	3.4	3.8	3.9
RR^a	1	2.04	1.36	1.40	
95% CI		0.9–4.9	0.4–4.2	0.5–3.8	

CI, Confidence interval.
^{a} RRs are adjusted for attained age, calendar year and sex. The estimated ERR/cGy was 0.11 (P = 0.05), with a 95% CI of 0.0–17.2.
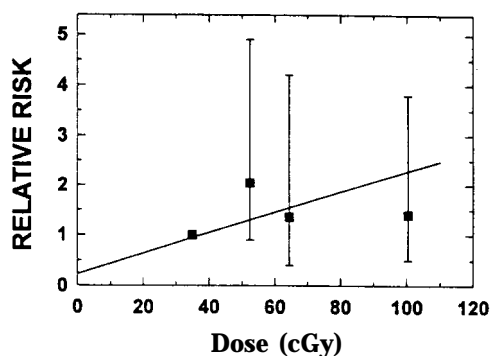
F<small>IG</small>, 2. Dose-response pattern for hyperparathyroidism. The *vertical position of each point* gives the relative risk for the dose category, and the *error bars* show the 95% confidence intervals. The *horizontal position of each point* gives the mean dose for each interval. The dose-response line was adjusted to pass through the point at 34.5 cGy, the mean dose for the less than 50 cGy group, which was used for comparison. The fitted regression line is relative risk = (1 + 0.11 x dose)/(1 + 0.11 x 34.9). The 95% confidence interval for ERR/cGy is 0.0, 17.2.

be monotonic, with a possible plateau above 50 cGy (Fig. 2). However, the confidence intervals for the individual relative risks are wide; therefore, it was not possible to compare alternative forms of the dose-response relationship.

Detailed analyses of variation in the dose-response curve were limited due to the small number of cases, but no statistically significant changes in the slope of dose-response relationship were seen as a function of gender, age at treatment, or three measures of time (attained age, years since treatment, and calendar year of diagnosis).

Discussion

We previously reported that the prevalence of hyperparathyroidism in this cohort, shown in Fig. 1 to approach 570, was higher than that in the general population (8). However, we were not able to exclude with certainty the possibility that this was due to ascertainment bias. Hyperparathyroidism is often asymptomatic, and its incidence increases with age (11). Although the study subjects have not been screened routinely with serum calcium determinations, they have been advised of their radiation exposure and have been screened for thyroid nodules. The large increase in the rate of hyperparathyroidism from before to after 1974, the year in which thyroid screening began, is probably due in part to increased medical attention. In the general population, the incidence of hyperparathyroidism is approximately 2-fold higher in women than in men (11). The equal rates observed in this cohort are consistent with an effect of radiation. The dose-response relationship observed in this study provides confirmation that radiation exposure can lead to hyperparathyroidism.

Among a subsample of almost 4000 clinically examined atomic bomb survivors, the overall ERR/cGy was 0.031, but the ERR/cGy for children aged 5 yr at the time of the bombing was 0.10 (l). In our study, which is limited to childhood exposure, we observed a very similar ERR/cGy, but we did not detect an effect of age at exposure. In the atomic bomb survivor study, the range of ages at exposure was from infancy to old age, and the results provide some evidence of a trend for decreasing risk with increasing age at exposure. As in our study, no difference in risk with gender was observed. Another study of atomic bomb survivors in Hiroshima Prefecture reported a significantly elevated risk of parathyroid tumors, ascertained from a tumor registry, diagnosed between 1974-1987 among persons proximally exposed to the bomb compared to a nonexposed population (12).

Although the magnitude of the excess relative risk (11 at 1.0 Gy) is substantial, the confidence interval for the dose-response estimate is broad. The similarity of the ERR/cGy in the clinically examined atomic bomb survivors lends support to our finding. However, the interpretation of these point estimates is uncertain because they are based on thyroid, rather than parathyroid, doses. In addition, as reported previously (7), there are uncertainties because rectangular fields were incompletely described as to whether they were oriented horizontally or vertically. On the other hand, it may be that the parathyroid glands, like the thyroid gland, are highly sensitive to radiation. Indeed, the magnitudes of the risk estimates are consistent with those observed for thyroid cancer in a pooled analysis of seven studies of childhood radiation exposure (Ron, E., *et al.,* in preparation) and for benign thyroid tumors in the Michael Reese Hospital cohort (7), a cohort of children irradiated for lymphoid hyperplasia in Boston (13), and children irradiated for tinea capitis in Israel (14).

In summary, the dose-response relationship provides evidence that radiation exposure causes hyperparathyroidism. Although some cases of hyperparathyroidism are asymptomatic and do not require surgery, others cause significant morbidity, including nephrolithiasis and metabolic bone disease, and can become life threatening (15). Therefore, calcium should be measured periodically and indefinitely (every 1–2 yr at the time of general checkups would be reasonable) in all individuals who have been exposed to head and neck radiation.

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